BIODEGRADABLE POLYMER COMPOSITION

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a division of U.S. patent application Ser. No. 07/783,512, filed Oct. 28, 1991, now U.S. Pat. No. 5,324,519 (issued Jun. 28, 1994), which is a continuation-in-part of U.S. patent application Ser. No. 384,416, filed Jul. 24, 1989, now U.S. Pat. No. 5,077,049 (issued Dec. 31, 1991), which applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Polymeric implants are useful as delivery systems and/or as mechanical barriers. Implants such as preformed membranes or films have been described. However, many of these implants have limited properties and produce inferior results either as mechanical barriers or delivery systems.

Several implant techniques have been used in medical and dental applications. One application of interest is the use of implants in treatment of periodontal disease. Surgery alone does not result in restoration of lost periodontium. Successful periodontal restoration is known to occur if periodontal ligament cells are allowed to colonize root surfaces preferentially over gingival epithelial cells, gingival fibroblasts or osteoblasts. Microporous membranes, such as the Millipore® filter and GORE-TEX® membranes, have been used for periodontal tissue regeneration. Typically, the periodontal flap is cut, and the membrane is surgically inserted to cover the surface of the tooth root and to physically occlude epithelial cells from apically migrating along the root surface.

Those membranes, however, have several drawbacks. Besides variable results, a second surgical entry is needed to remove the membrane after tissue regeneration has been achieved because the membranes are not biodegradable. There is also a higher incidence of infection in connection with their use.

To preclude surgical removal of the implant, membranes made of bioabsorbable material, such as microfibrillar collagen, polylactic acid, and polygalactin (Vicryl®) mesh have been used. Results have been variable, and the therapeutic effect of these membranes has been unpredictable. In addition, fitting and positioning these membranes to the implant site is time-consuming and cumbersome. The degradation time of membranes composed of collagen has been variable, and the risk of adverse immunological reaction to this foreign protein material in the body presents a major concern.

Therefore, an object of the invention is to provide a composition comprising a biodegradable or bioerodible polymer for use as an implant in an animal including a human. Another object is the development of an implant that will eliminate the need for its surgical removal after its purpose has been achieved. Another object is to provide a composition which may be administered to an implant site in liquid form and which is capable of solidifying in situ to form an implant. A further object of the invention is to provide a biodegradable implant which may be used to enhance connective cell or tissue growth and deter growth of epithelial cells and tissue into the core of the implant. Yet another object is to provide an implant which is capable of delivery of a drug or other medicament over a desired period of time. A further object is to provide an implant for

providing controlled release delivery of at least one biologically-active agent for stimulation and/or enhancement of physiological or biological activity in an animal.

SUMMARY OF THE INVENTION

These and other goals are achieved by the present invention which is directed to a composition for providing in situ a biodegradable or bioerodible microporous matrix. The matrix may be used to deliver biologically-active substances and/or for selective enhancement of cell growth and tissue regeneration in animals.

The composition is a liquid formulation of a biocompatible and biodegradable or bioerodible thermoplastic or thermoset polymer or copolymer which is substantially insoluble in aqueous media and body fluids. The composition may include a separate pore-forming agent which is capable of generating additional pores within the polymer matrix. When a biologically-active agent is to be released by the matrix, the agent is dissolved in the composition to form a homogenous solution or dispersed in the composition to form a suspension.

The invention also provides a method of using the composition for preventing and treating diseases and disorders, such as diseases of the bone and connective tissue, infectious diseases, cancer, metabolic disorders and allergies. The invention also provides a method of using the composition for tissue regeneration useful in wound and organ repair, nerve regeneration, periodontium regeneration, and bone regeneration. The invention also provides a method of using the composition for altering the physiological or biological activity of an animal such as reproductive function.

Thermoplastic polymer compositions

According to a first embodiment of the invention, the composition is a liquid formulation of a thermoplastic polymer and a pharmaceutically acceptable organic solvent. The composition is administered as a liquid to an implant site, whereupon the solvent diffuses or dissipates into the surrounding aqueous tissue fluids. The thermoplastic polymer is not soluble in these aqueous fluids so that it coagulates or solidifies to form a microporous solid or gelatinous matrix. The matrix preferably has a two-layered pore structure composed of a core portion and an outer surface layer or skin. The polymer matrix is suitable for use as an in situ formed implant in an animal, including humans and other mammals. The composition may be administered to tissue, to a surgical incision, or to a void space in tissue such as a periodontal pocket, and the like.

Thermoset polymer compositions

According to a second embodiment of the invention, the composition is a liquid formulation of a thermoset prepolymer or copolymer, preferably an acrylic ester-terminated biodegradable prepolymer, which is capable of cross-linking in situ to form a polymeric or copolymeric solid or gelatinous matrix. The composition preferably is a neat liquid but may include a pharmaceutically acceptable organic solvent that is miscible with water and body fluids.

When the thermoset polymer composition is cross-linked in situ, the resulting matrix is rendered microporous by one of several means. Use of a small but suitable amount of organic solvent will produce pores as described above for the thermoplastic polymer. The prepolymer ingredients may release a pore-forming moiety such as carbon dioxide and the like, or a separate pore-forming agent may be included. The pore-forming agent may be any suitable organic or inorganic substance which is soluble or substantially mis-